NIH Public Access
Author Manuscript
*J Pers Med*. Author manuscript; available in PMC 2014 June 10.

Published in final edited form as:
*J Pers Med*. ; 4(1): 1–19. doi:10.3390/jpm4010001.

# Design and Implementation of a Randomized Controlled Trial of Genomic Counseling for Patients with Chronic Disease

**Kevin Sweet**[1,2,*], **Erynn S. Gordon**[3,4], **Amy C. Sturm**[1,2], **Tara J. Schmidlen**[3], **Kandamurugu Manickam**[1,2], **Amanda Ewart Toland**[1], **Margaret A. Keller**[3,5], **Catharine B. Stack**[3,6], **J. Felipe García-España**[3], **Mark Bellafante**[3], **Neeraj Tayal**[7], **Peter Embi**[8], **Philip Binkley**[9], **Ray E. Hershberger**[1,9], **Wolfgang Sadee**[10], **Michael Christman**[3], and **Clay Marsh**[2]

[1] Division of Human Genetics, Ohio State University Wexner Medical Center, Columbus, OH 43420, USA

[2] Center for Personalized Health Care, Ohio State University Wexner Medical Center, Columbus, OH 43420, USA

[3] Coriell Institute for Medical Research, 403 Haddon Avenue, Camden, NJ 08103, USA

[4] Invitae, 458 Brannan Street, San Francisco, CA 94107, USA

[5] American Red Cross, 700 Spring Garden Street, Philadelphia, PA 19123, USA

[6] American College of Physicians, 190 N. Independence Mall West, Philadelphia, PA 19106, USA

[7] Department of Internal Medicine, Ohio State University College of Medicine, Columbus, OH 43420, USA; Neeraj.Tayal@osumc.edu

[8] Department of Bioinformatics, Ohio State University College of Medicine, Columbus, OH 43420, USA; Peter.Embi@osumc.edu

[9] Division of Cardiovascular Medicine, Ohio State University College of Medicine, Columbus, OH 43420, USA

[10] Program in Pharmacogenomics, Department of Pharmacology, The Ohio State University College of Medicine, Columbus, OH 43420, USA; Wolfgang.Sadee@osumc.edu

## Abstract

We describe the development and implementation of a randomized controlled trial to investigate the impact of genomic counseling on a cohort of patients with heart failure (HF) or hypertension (HTN), managed at a large academic medical center, the Ohio State University Wexner Medical

---

© 2014 by the authors

This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution license (http://creativecommons.org/licenses/by/3.0/).

[*] Author to whom correspondence should be addressed; Kevin.Sweet@osumc.edu; Tel.: +1-614-293-6694; Fax: +1-614-293-2314.. Amy.Sturm@osumc.edu (A.C.S.); Kandamurugu.Manickam@osumc.edu (K.M.); Amanda.Toland@osumc.edu (A.E.T.); Ray.Hershberger@osumc.edu (R.E.H.); Clay.Marsh@osumc.edu; erynn.gordon@invitae.com (E.S.G.); TSchmidl@coriell.org (T.J.S.); margaret.keller@redcross.org (M.A.K.); cstack@acponline.org (C.B.S.); fgarciaespana@coriell.org (J.F.G.-E.); mbellafante@coriell.org (M.B.); christman@coriell.org (M.C.); Philip.Binkley@osumc.edu

Conflicts of Interest
The authors declare no conflict of interest.

Center (OSUWMC). Our study is built upon the existing Coriell Personalized Medicine Collaborative (CPMC®). OSUWMC patient participants with chronic disease (CD) receive eight actionable complex disease and one pharmacogenomic test report through the CPMC® web portal. Participants are randomized to either the in-person post-test genomic counseling—active arm, *versus* web-based only return of results—control arm. Study-specific surveys measure: (1) change in risk perception; (2) knowledge retention; (3) perceived personal control; (4) health behavior change; and, for the active arm (5), overall satisfaction with genomic counseling. This ongoing partnership has spurred creation of both infrastructure and procedures necessary for the implementation of genomics and genomic counseling in clinical care and clinical research. This included creation of a comprehensive informed consent document and processes for prospective return of actionable results for multiple complex diseases and pharmacogenomics (PGx) through a web portal, and integration of genomic data files and clinical decision support into an EPIC-based electronic medical record. We present this partnership, the infrastructure, genomic counseling approach, and the challenges that arose in the design and conduct of this ongoing trial to inform subsequent collaborative efforts and best genomic counseling practices.

## Keywords

implementation; genomics; medicine; randomized; patients; counseling; actionable; risk perception; pharmacogenomics

## 1. Introduction

Genomic technologies are increasingly being utilized in the clinical setting and are expected to transform personalized approaches to medicine over the next decade. When genomic biomarkers are coupled with clinical information, family history, lifestyle, and other environmental factors, more informed predictions about risks for rare and common disease and response to therapeutics can be provided [1]. In addition, genomic information can be used to tailor screening and prevention strategies. While personalized medicine is still in the early stages of development, a number of academic medical centers and integrated health systems have already begun to use discrete genomic data for personalized clinical care [2–4]. However, the clinical implementation of large amounts of genomic information is emerging [5,6], and studies examining the effects of genomic counseling on this process have primarily focused on healthy motivated cohorts [1,7–9]. Hence, it is imperative to evaluate diverse populations of patients with chronic disease (CD), their understanding and response to actionable genomic risk information, related to and beyond their diagnosis, and to develop optimal methods for information delivery [10–13].

The Coriell Personalized Medicine Collaborative (CPMC®) is an ongoing longitudinal study, launched in December 2007, by the Coriell Institute for Medical Research to explore the core issues of utility and delivery of personalized medicine [14]. The Ohio State University Wexner Medical Center (OSUWMC) partnered with Coriell in 2009 to focus on the use and delivery of personalized medicine to a CD population. Specifically, this collaboration centered on recruitment of a new cohort of the CPMC® to investigate the impact of genomic counseling using a randomized controlled trial study design in patients with CD disease within an academic medical center environment. Patients with either a diagnosis of heart failure (HF) or hypertension (HTN) were selected because of high disease prevalence, frequent clinic visits, and long-term use of medications for disease management. All prospective CD participants were required to, (1) attend a one-hour informed consent and study education session, and (2) register on the CPMC® web portal through their home computer and complete CPMC® parent study surveys (demographics, medical history, family history, lifestyle, medications, medication reactions) and a baseline study specific survey. Genotyping was then performed. All participants were subsequently notified by email of the availability of an initial batch of results for eight health conditions (type 1 diabetes, type 2 diabetes, coronary artery disease, age-related macular degeneration, prostate cancer, melanoma, systemic lupus erythematous, and hemochromatosis) and one pharmacogenomic result (*CYP2C19* results interpreted in the context of response to clopidogrel) through the CPMC® web portal. To determine the impact of genomic counseling on outcomes, participants were block randomized to either receive in-person genomic counseling (active arm) or no genomic counseling (control arm). Active participants were offered in-person genomic counseling after viewing of at least one test report through the CPMC® web portal. The control arm was offered in-person genomic counseling after a three-month randomization period. Follow up OSUWMC-Coriell study specific surveys are then administered to both groups through the CPMC® web portal. Additional health condition and pharmacogenomic (PGx) reports are released over the course of study, along with additional parent CPMC® study surveys.

The primary study outcome is to determine whether there is a change in risk perception and understanding of test results for participants who receive in-person genomic counseling (active arm) *versus* those that will not (control arm) at baseline compared to follow-up. Study specific baseline and follow-up surveys measure risk perception, risk perception accuracy, general and relative risk numeracy, genetic knowledge, intention to change health behavior, acceptability of test result information, and other outcome measures related to the participant’s risk for the initial batch of results. We will measure satisfaction with genomic counseling and modifications to health behaviors over time. OSUWMC physicians were also recruited into a pilot study to explore their knowledge and test result utilization. Here we report on clinical implementation and study activities over the 28-month period, from 30 May 2011 to 31 September 2013. The study continues to collect follow-up data.

## 2. Methods

The parent CPMC® study was established as a prospective observational research study with ancillary randomized controlled trials seeking to determine the impact of multiplex genomic test results on health and health behavior when reported directly to study participants. It has also sought to understand best practices around the use of genomic information in medical settings and individual health management within three study cohorts: community, cancer, and CD. The community cohort participants were recruited without regard to health status or affiliation with a healthcare institution, while the cancer study group consists of participants with a personal history of either breast or prostate cancer. The CPMC® has been described in detail previously [14].

The OSUWMC-Coriell partnership and this study focused on the CD cohort, and the randomization of this cohort to assess the impact of genomic counseling on various study outcomes. To develop the necessary study related infrastructure, the educational pieces and infrastructure currently in place as part of the CPMC® parent study were adapted and transformed. This included customization of the CPMC® web portal to incorporate study-specific surveys, allowing access to study participant reports by the OSUWMC licensed genomic counselors, and randomization mechanisms. An encryption system allows for transfer of the DNA sample, the CPMC® test reports and phenotype/genotype data between institutions.

### 2.1. Participants

HF and HTN were chosen given the burden of these diseases and their prevalence (2.1% and 29.1% [15,16] (age-adjusted prevalence among U.S. adults aged 20 and over in 2010 and adults 18 and over in 2011–2012, respectively). Direct involvement of OSUWMC physicians was achieved through the identification of clinical champions to assist with patient recruitment. OSUWMC patient participants are required to be age 18 or older, have access to the Internet, and a diagnosis of either HF or HTN since the implementation of their EPIC® electronic medical record (EMR) system (06/2008).

### 2.2. Study Procedures

Patients were enrolled in the clinical setting by a trained study recruiter who administered a PowerPoint educational presentation on all aspects of the study including access to the CPMC® web portal, the randomization component, background information on DNA, genes, and single nucleotide polymorphisms, composition of the test reports, and the availability of genomic counseling. The participant then completed the informed consent process and a saliva sample was collected for DNA testing. Samples and consent documentation were sent to Coriell, and samples were accessioned and unique CPMC® web portal accounts created for each participant. All participants completed baseline on-line surveys (demographic, medical history, family history, lifestyle, medications, and study-specific) using the CPMC® web portal on their home computer. Online support was available if a participant had questions regarding access of the surveys through the CPMC® web portal, otherwise survey completion was unsupervised. Participants, however, will be prompted to review and update the data entered into the web portal periodically to provide longitudinal health data from which changes in health outcomes will be determined as part of the parent CPMC® study. Following completion of all baseline surveys, participants were block randomized to the active or control arm of the study. Each arm received the same nine personalized risk reports for their initial batch of test reports. Participants in the active arm received in-person genomic counseling, from one of two available licensed genomic counselors, within one month of viewing at least one report of the initial batch of nine reports. In contrast, subjects in the control arm were not offered genomic counseling as part of the study protocol, but were able to access in-person genomic counseling, if requested, three-months post-result viewing and post-follow up survey (study) completion (Figure 1).

### 2.3. Variants Returned

Genetic testing with Affymetrix 6.0 and DMETPlus GeneChips was performed only after participants completed the required baseline questionnaires. These GeneChip platforms were chosen to allow study of behavioral outcomes related to diseases affecting a reasonable proportion of all CPMC® study participants. Results reported to participants were limited to single nucleotide polymorphism (SNP) variants associated with complex diseases and drug-gene pairs deemed potentially actionable by Coriell's advisory boards—the Informed Cohort Oversight Board (ICOB) and the Pharmacogenomic Advisory Group (PAG) [14]. A potentially actionable condition is a condition for which the risk is likely to be mitigated by individual action (behavior or lifestyle) or by medical action (screening, preventive treatment or early intervention). The initial batch of results for the chronic disease cohort includes eight actionable diseases and one drug-gene pair (Table 1).

These eight health conditions were chosen in accordance to the Coriell Institute guiding principles for risk reporting: relative high frequency of the genetic variant used to assess risk; varied effect size of each variant on risk; and the finding that each condition has an actionable or potentially actionable component [17]. Most of these conditions are also highly prevalent in the general population. The *CYP2C19* report was the first drug-gene pair to be released through the CPMC®. The development of CPMC® risk reports has been described in detail previously [17]. Following the completion of the follow up assessment (post-genomic counseling for active arm and post-result viewing for control arm), additional approved personalized risk (Table 2) and drug response reports (Table 3) are prospectively released to OSUWMC-Coriell CD participants through the CPMC® web portal. This will allow for longitudinal assessment of health and health behavior through the parent CPMC® study.

### 2.4. Post-Test Genomic Counseling

Genetic counseling protocols for Mendelian disorders as well as those available in the context of multiplex genomic studies were reviewed and content areas catalogued to develop the design of the genomic counseling session [7,18–26]. The one-hour, in-person genomic counseling sessions provide individualized risk assessment using the nine personalized CPMC® study reports, collection of at least a three-generation pedigree, as well as evaluation of the patient's medical history, social history, pertinent environmental risk information, and current health promotion and screening behaviors. Prior to the genomic counseling session, the patient's medical history is extracted from the OSUWMC EMR, and the family history entered into the CPMC® web portal by the patient is extracted to develop a pedigree. As the genomic counseling sessions were designed to review results for all nine personalized reports, these are also accessed. This individual patient information is then assessed by the OSUWMC genomic counselor in conjunction with the OSUWMC medical geneticist. The design of the parent study CPMC® test reports (Figure 2) present risk as relative risk for each condition, for genetic and non-genetic (lifestyle; environmental) risk factors in both graphical and numeric form [17]. These reports also provide estimates of risk in the general population as a reference point. To aid explanation and contrast, and given the amount of information that must be presented in the one-hour counseling session, we developed a tabular visual display for all eight disease reports and the *CYP2C19* report. The tabular display synthesizes each of these factors into a one-page document to provide an overall “quick reference” summary of risk, and comparison of the patient's risk to the general population. At least one CPMC report is also assessed “live” via the web portal during the session to associate with the tabular display. There is active discussion as to the essential risk factors each patient has for a given disease, to include additional disease risks that may have been identified by additional review of the family history. There is discussion to gauge what actions the patient might take to prevent or lower risk for development of a given disease. Post-session, the details of the risk assessment and the updated medical and family history is reviewed in conjunction with the medical geneticist. A risk summary research report (Figure 3), which provides focused interpretation for each of the nine personalized CPMC® study reports, as well as recommendations based on this assessment and the medical and family history, is then generated. This risk summary report is mailed to the patient participant, and made available to the OSUWMC health care team through the EMR.

### 2.5. Study-Specific Surveys

Study-specific baseline and follow up surveys were designed to measure perceived personal risk, risk perception accuracy, general and relative risk numeracy, genetics/genomics knowledge, intention to change health behavior, personalized medicine perceptions and genomics awareness, information-seeking preferences and behaviors, acceptability of test result information, family communication, perceived utility, and genomic counseling satisfaction (if randomized to that arm) [1,18,20,27–32] (Supplementary Files 1 and 2). Additional optional disease specific outcome surveys are sent to participants through the web portal three months after they view each result to measure result recall, sharing of results with family and health care providers, behavioral and lifestyle changes, and physician recommendations [14]. We can also monitor the OSUWMC EMR to determine potential outcomes on various measures and medical recommendations to elucidate changes in actual behavior during the course of study on this patient-based population.

### 2.6. Clinical Implementation (Physicians and the EMR)

OSUWMC physicians were recruited into a pilot study of their knowledge and result utilization. Two physician champions, one each from Cardiovascular Medicine (CVM), and General Internal Medicine (GIM) were identified, and internal group meetings with the respective physican teams arranged. The investigators designed an educational module consisting of an in-person lecture on genetics, genomics, pharmacogenomics, case examples, and study details including the randomization component, the makeup and availability of the CPMC® test reports in the EMR, and a question and answer session. In addition, the physicians were informed of the availability of the study genomic counselors and medical geneticists for consult regarding their patients’ CPMC® test reports. Interested physicians completed an informed consent document, a study survey adapted from Roederer and colleagues [33] related to their awareness of genomic medicine and perception of clinical utility, and worked with study staff to recruit eligible patients.

Clinical implementation of the OSUWMC EPIC-based EMR system occurred during the development of this study that necessitated the development of new processes. Each

CPMC® report was labeled with a naming standard with separate creation of a new procedure code for direct uploading to the EMR. The reports are accessible by any OSUWMC physician through hyperlinks to the report content via the EPIC/Labs tab. Patient participants seen for genomic counseling subsequently receive a risk summary research report (Figure 3), which was also routed directly to their physician participant through the EMR system. Non-participant physicians are also able to access the patient risk summary research report, and the CPMC® test reports in the EMR.

### 2.7. Approach to Statistical Analysis

The statistical analysis will proceed in several distinct phases, from generating descriptive summaries, graphical representations to identify outliers, to performing inferential analyses. Survey questions will be categorized by using summary indexes such as the genetic knowledge score, the relative risk numeracy index, and the benefits of the OSUMC-CPMC study score. In addition, factor analytic techniques will be used to categorize outcomes. Descriptive statistics, such as means, standard deviations, medians and range for continuous variables (e.g., age, length of time to receive genomic counseling, length of time between baseline and follow-up surveys, numbers of risk reports viewed by the participant, genetic knowledge score), and percentages for categorical variables (e.g., gender, race, education, income) will be generated for quantitative data. These statistics will be generated for all quantitative data on the CD cohort, by genomic counseling group (active *versus* control), disease group (HF *versus* HTN) and relevant subgroups of interest. Histograms and box plots will be the graphical measures used to complement descriptive analyses of categorical data. Relevant continuous measures will be evaluated for normality and those differing markedly from normality will be summarized by using medians, interquartile ranges, and box-plots. In addition, response variables that violate assumptions of normality will be transformed to achieve normality or analyzed using nonparametric statistics. For statistical inference, we will employ a variety of parametric and non-parametric statistical techniques such as t-test, chi-square, Fisher's exact test, Wilcoxon rank sum test, Person-r, Spearman-rho or point- biserial correlations, linear and non-linear regression analysis, random effects models, generalized estimating equations, factor analysis, and structural equation modeling. For analyses involving small sample sizes, exact statistical tests and bootstrap methods will be applied.

Overall differences in risk perception and other outcome measures between the active and the control groups will be assessed. The analyses will adjust for relevant covariates such as CD group (HF *versus* HTN), sex, race, education, income, occupation, number of risk reports viewed, genomic counselor, and others found to differ significantly between groups (*i.e.*, confound) when comparing treatment conditions (active *versus* control) on baseline characteristics. We will consider analyses based upon (1) all randomized subjects (commonly called the intention-to-treat population); and (2) excluding those who were non-compliant. The statistical tests will be two-sided with a type-I error of 0.05.

In addition, exploratory analyses to evaluate the effect of counseling by genetic and non-genetic risk (high *versus* low) interaction will be evaluated. Such interactions will help us understand if between-counseling group differences in outcome measures vary by genetic risk group. Exploratory analyses will also be performed to describe the baseline knowledge of study physicians regarding genomic testing for common complex disease and the clinical utility and integration of genomic information into electronic medical records during the course of the study.

A total of 252 patients (126 patients each in the active and control arms), provides 80% power to detect differences in changes in overall risk perception of 0.5 points (on a 5 point scale) and greater. For example, if the change in overall risk perception is 0 (no change) in the group without genomic counseling (control arm), then we would be able to detect as significantly different, changes in the counseling group (active arm) of −0.5 or smaller, and of +0.5 or greater. These estimates assume a standard deviation for change score of 1.5 (based upon internal preliminary data for three-month overall perceived risk of type 2 diabetes) and two-sided tests with $\alpha = 0.05$.

## 3. Results

### 3.1. Patient Recruitment/Counseling

Of 252 patient participants accrued as of October of 2013, 210 have completed the required baseline questionnaires (Table 4). Forty-two of the patients provided consent but failed to complete the required baseline surveys, and, thus, were removed from study. All 210 have received their initial batch of nine personalized CPMC® test reports, with equal randomization into the active (105) and control (105) arms. In the active group, 73 out of 105 participants have received genomic counseling. Nine out of 105 have received in-person genomic counseling in the control group.

### 3.2. Physician Recruitment

Twenty General Internal Medicine (GIM) and Cardiovascular Medicine (CVM) physicians participated in the pilot study (57%; 12/27 GIM; 8/8 CVM), completing pre-post education genetics knowledge assessment, attending an in-person educational module, and working with study staff to recruit patients into the study. The fifteen GIM physicians who declined participation cited lack of time, concerns with having to act on the results for their patients (*i.e.*, screen for coronary artery disease if the patient participant had a SNP risk variant), and perceived lack of clinical utility after the initial educational intervention. As the study design required a sufficient number of physicians to be involved in order to accrue patients, a third clinical area, the Department of Family Medicine (FM) was added in October 2012. An alternate approach was developed for patient recruitment utilizing an internal FM recruitment team. Interested FM physicians could become “physician participants”, as with the GIM/CVM group, but instead of an in-person educational module, a one-hour educational webinar accredited by OSUWMC for a maximum of 1.5 AMA PRA Category 1 Continuing Medical Education Credit(s)™ was made available. Although 16 FM physicians subsequently provided access to patients for recruitment, none completed the educational program or pre-post education knowledge assessment.

## 4. Discussion

In this report we detail the design and implementation of a prospective randomized controlled trial to investigate the impact of in-person genomic counseling in the return of actionable genomic information for complex disease and pharmacogenomics. Specifically, patients with chronic disease managed in an academic medical center received genomic results through the CPMC®-Coriell web-portal, and were randomized to additional in-person post-test genomic counseling *versus* only the web-based return of results. This academic institution-private non-profit partnership is among the first coordinated efforts to implement genomic information, including pharmacogenomic information, into patient care to permit such a study to be undertaken.

The strengths of an academic medical center include access to patients and their clinical data, robust EMR and clinical support systems, clinician scientists, expertise with human genetics, and insightful pharmacy and pharmacogenomics support. In our view these strengths outweigh the limitations and challenges of the academic medical center environment, which include institutional inertia, fragmented expertise and the lack of appreciation and acceptance by clinicians to enact genomic guided medicine [6,9,13,18]. These challenges were met with dedicated involvement of senior leadership, active engagement of physician champions and other vested parties (*i.e.*, pharmacogenomics), and integration of genetic counselors and geneticists to establish the protocol, and processes for data return and infrastructure development. The existing CPMC® infrastructure provided key strengths, including experience with genomic based protocols and consent processes, CLIA-compliant genotyping, internal oversight boards to define actionable conditions, and an interactive web portal for direct delivery of participant results. Internal pilot funding from both organizations catalyzed project initiation. Through internal meetings, teleconferences and other interactions including travel to the partner institute, the partnership has evolved into a coordinated effort that takes advantage of the diversity and strengths of each institution. Limitations, such as privacy concerns for sharing medical records and genomic data, and the incorporation of outside genomic test reports into the EMR, were overcome by active involvement of interdisciplinary IT workgroups and legal teams. Significant infrastructure was developed that allows confidential sharing of data between institutions, specifically, direct release of the initial study results for uploading to the EMR (and prospectively for new test reports); extraction of clinical data from the EMR; and transfer of the genomic datasets. Lastly, modification of an existing comprehensive consent document addressed many of the confidentiality concerns present in prospective genomic-based research.

Patient participants consented to genomic testing with the understanding that the GeneChips utilized test for over one million single SNP sites of variation, but that the study results would only be released for variants associated with actionable health conditions approved by the ICOB and PAG [14]. This concept of consenting to limited and yet unknown information has not been routinely used outside of the CPMC® and raised unique issues related to participant expectations [34]. However, participants were informed that they will have access to all approved CPMC® results, and the option to view or not view each result independently. In addition, participants have been empowered, as part of the consent process, to indicate or deny their consent for sharing of data (genomic/phenotypic) with for-profit and non-profit third party researchers. The consent document, thus, provides what is now referred to as tiered-layered-staged consent [35]. Tiered consent allows study participants choices about the future use of their specimen beyond the initial study, as is often practiced in biobank research [22]. Layered consent involves providing only information (results) pertinent to the particular study, and providing this to all study participants; new results are then made available (layered) for access by the individual. Staged consent involves the element of time, which in this study was provided at two separate points: baseline (for enrollment purposes), and when the participant opts to view specific test reports via the CPMC® web portal (both from the initial batch of results, and prospectively). Patient participants also signed a separate, subject information sheet which allowed investigators access to discrete phenotypic information extracted from the EMR and for that information as well as genomic data to be shared between institutions.

Integral to the clinical genomic translation process is effective use of EMR applications to assist the physician team at the point of care. This component involved construction of IT applications for an existing EPIC-based EMR. Test results were transmitted from Coriell to OSUWMC in PDF format, in a secure manner, labeled with the appropriate disease/PGx name (*i.e.*, Coriell Report—Plavix) and made available to the OSUWMC physician team in the EMR. However, the length and format of the CPMC® test reports did not lend themselves well to rapid interpretation or automated clinical decision support platforms [36]. To address this concern, study design modification supported the use of the genomic variant information as a foundation for development of EMR-based clinical decision support (CDS) platforms [37,38]. Currently under development, these applications are based on discrete data points (*i.e.*, SNPs). They will incorporate information from the patient's EMR such as medications combined with the genomic variant data to trigger “best practice alerts” defined via conventional logical assertions. The first CDS algorithm under development is that for *CYP2C19* variants, and will include, over time, additional CDS capabilities, based on the potential adverse effect, such as recommending against the use of a certain medication [38].

Given our interest in evaluating physician use of genomic results, OSUWMC physicians were recruited into a pilot study of knowledge and result utilization. Many of the GIM and CVM physicians who chose study participation have become active partners, with studies looking at result utilization for patient care underway. We believe the low response rate for study participation on the part of other physicians, such as those in the FM group, can be interpreted in multiple ways. Lack of time, as suggested by the GIM physicians who also declined involvement; lack of interest in genetics; lack of interest in research; or concern about data that could be gleaned from participation (e.g., lack of genetic knowledge; clinical utility). More research is needed on barriers to physician participation in a study like this, especially since emerging technologies will allow more individuals access to their genomic profiles and primary care physicians, in particular, will become more involved in communicating risk information [1,8,12,13,35,39].

Genomic tests that analyze large sets of markers across the genome for multiple diseases and PGx variants continue to proliferate [1,5,6,9]. Although these offerings may vary, many of the disease susceptibilities conveyed are for common and complex disease, and for which the genetic contribution may explain only part of the disease burden. It is speculated that being told about genetic risk of complex disease might cause individuals to overestimate the probability of developing disease. This might generate unnecessary worry, anxiety, risk, and expense [29,40], although some studies suggest otherwise [1,8,41,42]. To mitigate these concerns, genomic counseling can be employed to adequately and effectively interpret and communicate the benefits, risks, and limitations [43], and assist with interpretation and education. Although preliminary data suggest that the uptake of genomic counseling is low (10%–15%) [7,22,42] understanding participant needs may help increase utilization [12]. Whether individuals who receive genomic information act on their results also requires further exploration. This is particularly true in diverse patient-based populations who have, to date, limited access or uptake of genomic testing for complex disease, and are likely to be different in many ways from the healthy, well-educated "early adopters" studied thus far [1,8,10]. In this study, patient participants receive education on the genotyping and SNP results and provide informed consent prior to testing, with extensive educational information (text; video) for each disease report made available through the CPMC® web portal. The randomization component, therefore, allows opportunity to study the utility of post-test in-person genomic counseling *versus* only the web-based return of results; to test our hypothesis of a significantly greater change in risk perception and understanding of test results for participants who receive in-person genomic counseling (active arm) as compared to those who do not (control arm). Our approach to development of the genomic counseling protocol was multifaceted, using literature review and feedback from the CPMC® genomic counselors, who have had extensive experience providing phone genomic counseling to CPMC® community participants. Indeed, rather than only focusing on the disease or PGx reports of interest to the participant, the in-person sessions were designed to review results for all nine personalized reports. To aid explanation, and given the amount of information discussed, we developed and incorporated a tabular visual display for all eight disease reports and the *CYP2C19* report into these patient sessions, with added discussion of variants associated with an increased risk (risk variants), decreased risk (protective variants), or those with no clinical impact. The tabular display used in the in-person counseling session synthesizes each of the risk factors into a one-page document to provide an overall "quick reference" summary. There is additional counseling for the *CYP2C19* result, which includes education regarding their specific haplotype (e.g., *CYP2C19**1/*3* or **2/*2*), metabolizer type, and an explanation of the indications for prescription of the relevant medication(s) (e.g., clopidogrel) [44]. The CPMC® risk reports are also accessed live via the web portal during sessions to assist participants in understanding how to navigate their results moving forward. This also presents an opportunity for "teachable moments" to enforce key concepts (*i.e.*, heritability, importance of modifiable risk factors). How patients with chronic disease cognitively engage and react to this information; their perceived susceptibility and methods of coping given they already have a chronic condition; their approach to decision-making and on how best to utilize information for which they may have no prior experience; and what they may want and need from the process of genomic counseling are areas of address. As there is need for more scalable and streamlined delivery models for common complex disease, this collaborative effort allows for prospective comparison of the CD and community CPMC® cohorts, and to study the effects of genomic counseling on risk perception, knowledge retention and behavior change. This may also allow results from this controlled-trial to be explored for generalizability to other populations. Additional identification of risk and subsequent referral for appropriate medical services (*i.e.*, nutritional counseling), and follow through on EMR referrals is being closely monitored, to determine whether any new referrals are dependent upon the genomic counseling assessment *versus* initiated independently by the patient's physician.

## 5. Conclusions

Genetic counseling, like other medical professions must continue to evolve and adapt to ever increasing amounts of data, and effectively translate this data to the lay person. This randomized controlled trial is among the first coordinated efforts to implement genomic information, including pharmacogenomic information, into patient care, and to investigate the impact of in-person genomic counseling in the return of actionable genomic results for common complex disease. This study will provide critical insights into the impact of genomic counseling on behavior and health, and enable the design of larger trials. It will allow for preliminary practice recommendations regarding best practices to facilitate comprehension of genomic test results, accurate risk perception, and to motivate behavior change. It will also promote further development of genomic counseling models and delivery methods. Patient response to pharmacogenomic testing, the myriad issues surrounding physician education and integrating effective clinical decision support to providers through the EMR are also areas of future research interest.

## Acknowledgments

We thank Regina Dudzik, Amy Ehrlich, Sofia Durrani, Anna Salikhova, Meagan Kane, Sarah Adelsperger, Elizabeth Baack, and Samantha DeMarsh, for their assistance with this study. The CPMC® study would not be possible without the efforts of a team of scientists and staff including: Neda Gharani, Joseph Jarvis, Daniel Lynch, Lisa Wawak, Rachel Kasper Norman Gerry, Courtney Kronenthal, Susan Delaney, Leo Lnu, and Corey Zuares.

Research reported in this publication was supported by the National Human Genome Research Institute of the National Institutes of Health under Award Number R21HG006575. This work was also supported in part by Grant U01 GM92655 and a subaward for the Translational Pharmacogenomics Project (TPP) via U01 HL105198 Pharmacogenomics of anti-platelet intervention-2 (PAPI-2) from NHLBI; and the OSUWMC Comprehensive Cancer Center. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

The Coriell Personalized Medicine Collaborative was funded by the William G. Rohrer Foundation, the RNR Foundation and a grant from the endowment of the Coriell Institute for Medical Research.

## References

1. Kaphingst KA, McBride CM, Wade C, Alford SH, Reid R, Larson E, Baxevanis AD, Brody LC. Patients’ understanding of and responses to multiplex genetic susceptibility test results. Genet. Med. 2012; 14:681–687. [PubMed: 22481132]
2. Dong H, Wang S. Exploring the cancer genome in the era of next-generation sequencing. Front. Med. 2012; 6:48–55. [PubMed: 22460448]
3. Pinto N, Cohn SL, Dolan ME. Using germline genomics to individualize pediatric cancer treatments. Clin. Cancer Res. 2012; 18:2791–2800. [PubMed: 22589487]
4. Ingelman-Sundberg M, Sim SC. Pharmacogenetic biomarkers as tools for improved drug therapy; emphasis on the cytochrome p450 system. Biochem. Biophys. Res. Commun. 2010; 396:90–94. [PubMed: 20494117]

5. Korf BR, Rehm HL. New approaches to molecular diagnosis. JAMA. 2013; 309:1511–1521. [PubMed: 23571590]
6. Manolio TA, Chisholm RL, Ozenberger B, Roden DM, Williams MS, Wilson R, Bick D, Bottinger EP, Brilliant MH, Eng C, et al. Implementing genomic medicine in the clinic: The future is here. Genet. Med. 2013; 15:258–267. [PubMed: 23306799]
7. Schmidlen, T.; Gordon, ES.; Christman, MF. Genomic Literacy: Emerging themes among genetic counseling inquiries from participants of the Coriell personalized medicine collaborative.. Proceedings of the 28th Annual Education Conference of the National Society of Genetic Counselors; 12–15 November 2009; Atlanta, GA, USA:
8. James KM, Cowl CT, Tilburt JC, Sinicrope PS, Robinson ME, Frimannsdottir KR, Tiedje K, Koenig BA. Impact of direct-to-consumer predictive genomic testing on risk perception and worry among patients receiving routine care in a preventive health clinic. Mayo Clin. Proc. 2011; 86:933–940. [PubMed: 21964170]
9. Darst B, Madlensky L, Schork N, Topol E, Bloss C. Perceptions of genetic counseling services in direct-to-consumer personal genomic testing. Clin. Genet. 2013; 84:335–339. [PubMed: 23590221]
10. McBride CM, Bowen D, Brody LC, Condit CM, Croyle RT, Gwinn M, Khoury MJ, Koehly LM, Korf BR, Marteau TM, et al. Future health applications of genomics: Priorities for communication, behavioral, and social sciences research. Am. J. Prev. Med. 2010; 38:556–565. [PubMed: 20409503]
11. Green ED, Guyer MS. Charting a course for genomic medicine from base pairs to bedside. Nature. 2011; 470:204–213. [PubMed: 21307933]
12. Lautenbach DM, Christensen KD, Sparks JA, Green RC. Communicating genetic risk information for common disorders in the era of genomic medicine. Annu. Rev. Genomics Hum. Genet. 2013; 14:491–513. [PubMed: 24003856]
13. Lehmann LS, Kaufman DJ, Sharp RR, Moreno TA, Mountain JL, Roberts JS, Green RC. Navigating a research partnership between academia and industry to assess the impact of personalized genetic testing. Genet. Med. 2012; 14:268–273. [PubMed: 22241103]
14. Keller M, Gordon ES, Stack CB, Gharani N, Sill CJ, Schmidlen TJ, Joseph M, Pallies J, Gerry NP, Christman MF. The Coriell personalized medicine collaborative: A prospective study of the utility of personalized medicine. Pers. Med. 2010; 7:301–317.
15. Nwankwo T, Yoon SS, Burt V, Gu Q. Hypertension among adults in the United States: National health and nutrition examination survey, 2011–2012. NCHS Data Brief. 2013; 133:1–8. [PubMed: 24171916]
16. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, et al. Heart disease and stroke statistics—2013 update: A report from the American Heart Association. Circulation. 2013; 127:e6–e245. [PubMed: 23239837]
17. Stack CB, Gharani N, Gordon ES, Schmidlen T, Christman MF, Keller MA. Genetic risk estimation in the coriell personalized medicine collaborative. Genet. Med. 2011; 13:131–139. [PubMed: 21233721]
18. Sanderson SC, O'Neill SC, White DB, Bepler G, Bastian L, Lipkus IM, McBride CM. Responses to online gstm1 genetic test results among smokers related to patients with lung cancer: A pilot study. Cancer Epidemiol. Biomark. Prev. 2009; 18:1953–1961.
19. Payne K, Nicholls S, McAllister M, Macleod R, Donnai D, Davies LM. Outcome measurement in clinical genetics services: A systematic review of validated measures. Value Health. 2008; 11:497–508. [PubMed: 18489673]
20. DeMarco TA, Peshkin BN, Mars BD, Tercyak KP. Patient satisfaction with cancer genetic counseling: A psychometric analysis of the genetic counseling satisfaction scale. J. Genet. Couns. 2004; 13:293–304. [PubMed: 19736695]
21. Bloss CS, Darst BF, Topol EJ, Schork NJ. Direct-to-consumer personalized genomic testing. Hum. Mol. Genet. 2011; 20:R132–R141. [PubMed: 21828075]
22. Gordon ES, Griffin G, Wawak L, Pang H, Gollust SE, Bernhardt BA. “It's not like judgment day”: Public understanding of and reactions to personalized genomic risk information. J. Genet. Couns. 2012; 21:423–432. [PubMed: 22180182]

23. Gollust SE, Gordon ES, Zayac C, Griffin G, Christman MF, Pyeritz RE, Wawak L, Bernhardt BA. Motivations and perceptions of early adopters of personalized genomics: Perspectives from research participants. Public Health Genomics. 2012; 15:22–30. [PubMed: 21654153]
24. Vassy JL, O'Brien KE, Waxler JL, Park ER, Delahanty LM, Florez JC, Meigs JB, Grant RW. Impact of literacy and numeracy on motivation for behavior change after diabetes genetic risk testing. Med. Decis. Making. 2012; 32:606–615. [PubMed: 22247420]
25. Smerecnik CM, Mesters I, Verweij E, de Vries NK, de Vries H. A systematic review of the impact of genetic counseling on risk perception accuracy. J. Genet. Couns. 2009; 18:217–228. [PubMed: 19291376]
26. Kasparian NA, Wakefield CE, Meiser B. Assessment of psychosocial outcomes in genetic counseling research: An overview of available measurement scales. J. Genet. Couns. 2007; 16:693–712. [PubMed: 17694397]
27. Kaphingst KA, Kreuter MW, Casey C, Leme L, Thompson T, Cheng MR, Jacobsen H, Sterling R, Oguntimein J, Filler C, et al. Health literacy index: Development, reliability, and validity of a new tool for evaluating the health literacy demands of health information materials. J. Health Commun. 2012; 17:203–221. [PubMed: 23030571]
28. Berkenstadt M, Shiloh S, Barkai G, Katznelson MB, Goldman B. Perceived personal control (ppc): A new concept in measuring outcome of genetic counseling. Am. J. Med. Genet. 1999; 82:53–59. [PubMed: 9916844]
29. Cameron LD, Muller C. Psychosocial aspects of genetic testing. Curr. Opin. Psychiatry. 2009; 22:218–223. [PubMed: 19553879]
30. Senay I, Hensley Alford S, Kaphingst KA. Judging risk for multiple diseases: The role of disease worry. J. Health Psychol. 2013; 18:554–560. [PubMed: 22843634]
31. Waxler JL, O'Brien KE, Delahanty LM, Meigs JB, Florez JC, Park ER, Pober BR, Grant RW. Genetic counseling as a tool for type 2 diabetes prevention: A genetic counseling framework for common polygenetic disorders. J. Genet. Couns. 2012; 21:684–691. [PubMed: 22302620]
32. Lipkus IM, Samsa G, Rimer BK. General performance on a numeracy scale among highly educated samples. Med. Decis. Making. 2001; 21:37–44. [PubMed: 11206945]
33. Roederer M, van Riper M, Valgus J, Knafl K, McLeod H. Knowledge, attitudes, and education of pharmacists in North Carolina regarding pharmacogenetic testing. Pers. Med. 2012; 9:19–27.
34. Kohane IS, Mandl KD, Taylor PL, Holm IA, Nigrin DJ, Kunkel LM. Medicine. Reestablishing the researcher-patient compact. Science. 2007; 316:836–837. [PubMed: 17495156]
35. Bunnik EM, Janssens AC, Schermer MH. A tiered-layered-staged model for informed consent in personal genome testing. Eur. J. Hum. Genet. 2013; 21:596–601. [PubMed: 23169494]
36. Masys DR, Jarvik GP, Abernethy NF, Anderson NR, Papanicolaou GJ, Paltoo DN, Hoffman MA, Kohane IS, Levy HP. Technical desiderata for the integration of genomic data into electronic health records. J. Biomed. Inform. 2012; 45:419–422. [PubMed: 22223081]
37. Payne PR, Borlawsky TB, Rice R, Embi PJ. Evaluating the impact of conceptual knowledge engineering on the design and usability of a clinical and translational science collaboration portal. AMIA Summits Transl. Sci. Proc. 2010; 2010:41–45. [PubMed: 21347146]
38. Shuldiner AR, Relling MV, Peterson JF, Hicks K, Freimuth RR, Sadee W, Pereira NL, Roden DM, Johnson JA, Klein TE. The pharmacogenomics research network translational pharmacogenetics program: Overcoming challenges of real-world implementation. Clin. Pharmacol. Ther. 2013; 94:207–210. [PubMed: 23588301]
39. Sweet, K.; Michaelis, R. The Busy Physician's Guide to Genetics, Genomics and Personalized Medicine. 1st ed.. Springer Verlag Press; London, UK: 2011.
40. Wasson K, Cook ED, Helzlsouer K. Direct-to-consumer online genetic testing and the four principles: An analysis of the ethical issues. Ethics Med. 2006; 22:83–91. [PubMed: 17115513]
41. Green RC, Roberts JS, Cupples LA, Relkin NR, Whitehouse PJ, Brown T, Eckert SL, Butson M, Sadovnick AD, Quaid KA, et al. Disclosure of APOE genotype for risk of Alzheimer's disease. N. Engl. J. Med. 2009; 361:245–254. [PubMed: 19605829]
42. Bloss CS, Schork NJ, Topol EJ. Effect of direct-to-consumer genomewide profiling to assess disease risk. N. Engl. J. Med. 2011; 364:524–534. [PubMed: 21226570]

43. Collins FS, Guttmacher AE. Genetics moves into the medical mainstream. JAMA. 2001; 286:2322–2324. [PubMed: 11710899]
44. Sturm AC, Sweet K, Manickam K. Implementation of a clinical research pharmacogenomics program at an academic medical center: Role of the genetics healthcare professional. Pharmacogenomics. 2013; 14:703–706. [PubMed: 23651015]

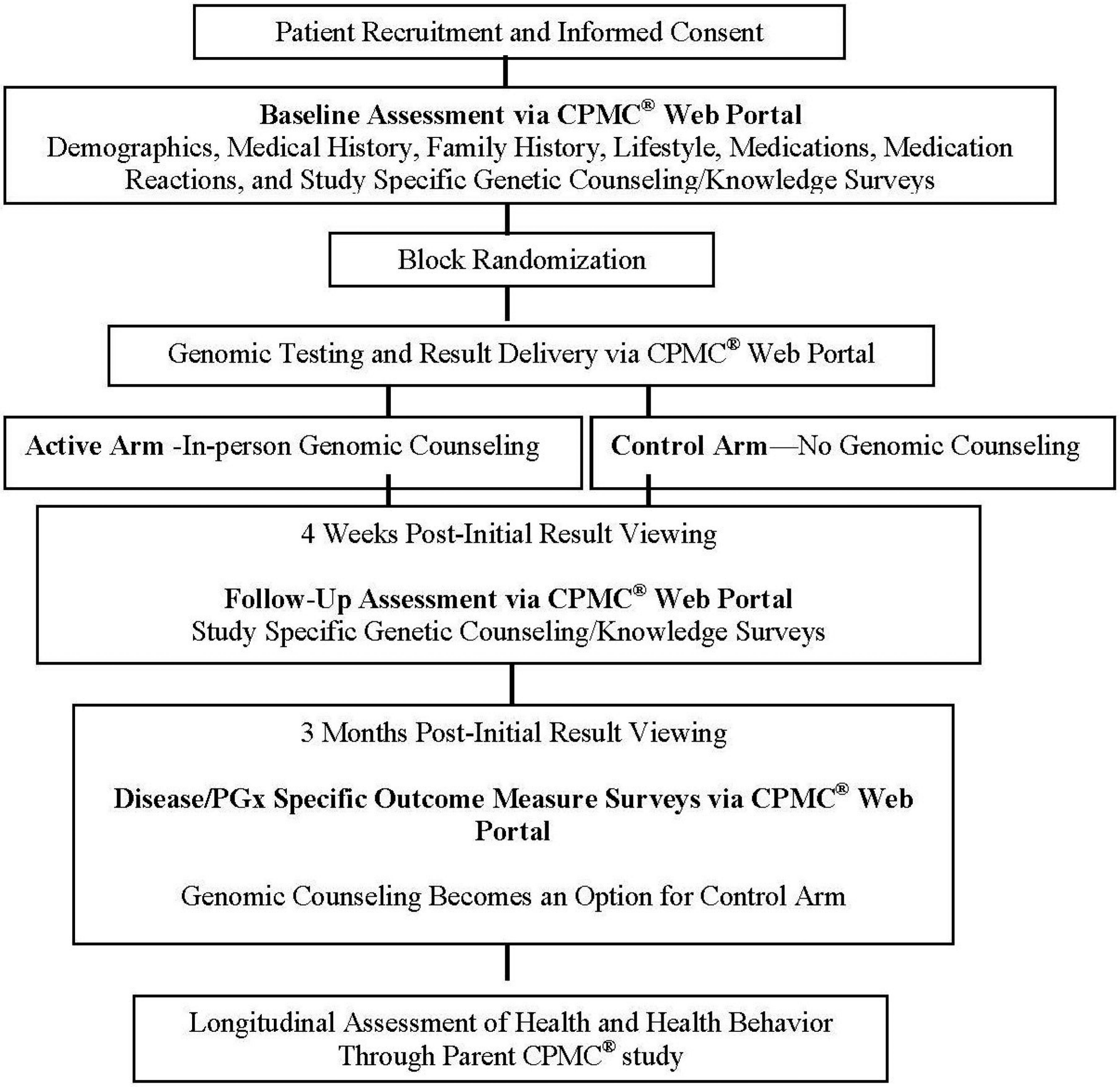
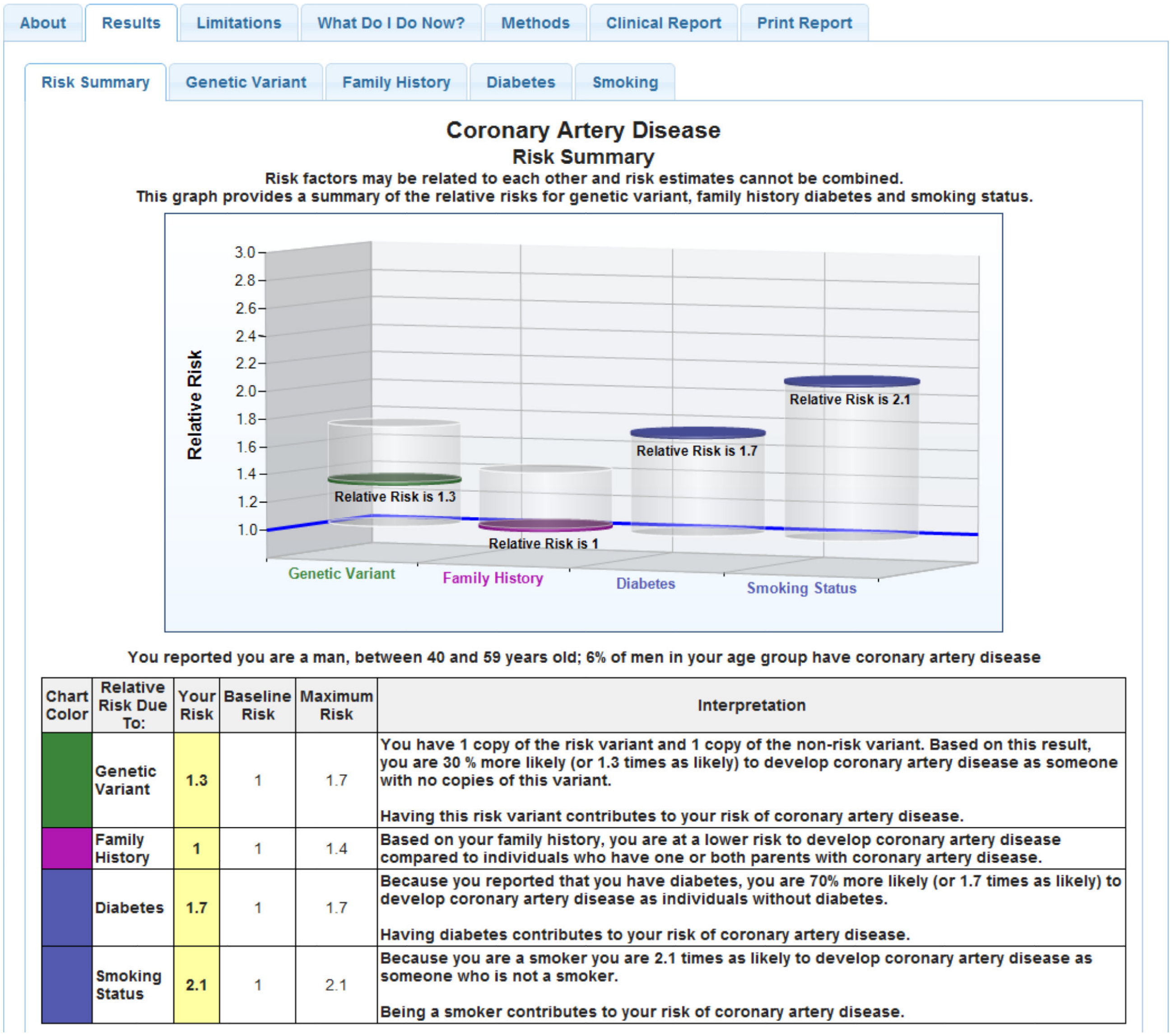

Patient Recruitment and Informed Consent
Baseline Assessment via CPMC® Web Portal
Demographics, Medical History, Family History, Lifestyle, Medications, Medication Reactions, and Study Specific Genetic Counseling/Knowledge Surveys
Block Randomization
Genomic Testing and Result Delivery via CPMC® Web Portal
Active Arm -In-person Genomic Counseling
Control Arm—No Genomic Counseling
4 Weeks Post-Initial Result Viewing
Follow-Up Assessment via CPMC® Web Portal
Study Specific Genetic Counseling/Knowledge Surveys
3 Months Post-Initial Result Viewing
Disease/PGx Specific Outcome Measure Surveys via CPMC® Web Portal
Genomic Counseling Becomes an Option for Control Arm
Longitudinal Assessment of Health and Health Behavior Through Parent CPMC® study

**Figure 1.**

Study schema.



**Coronary Artery Disease**

**Risk Summary**

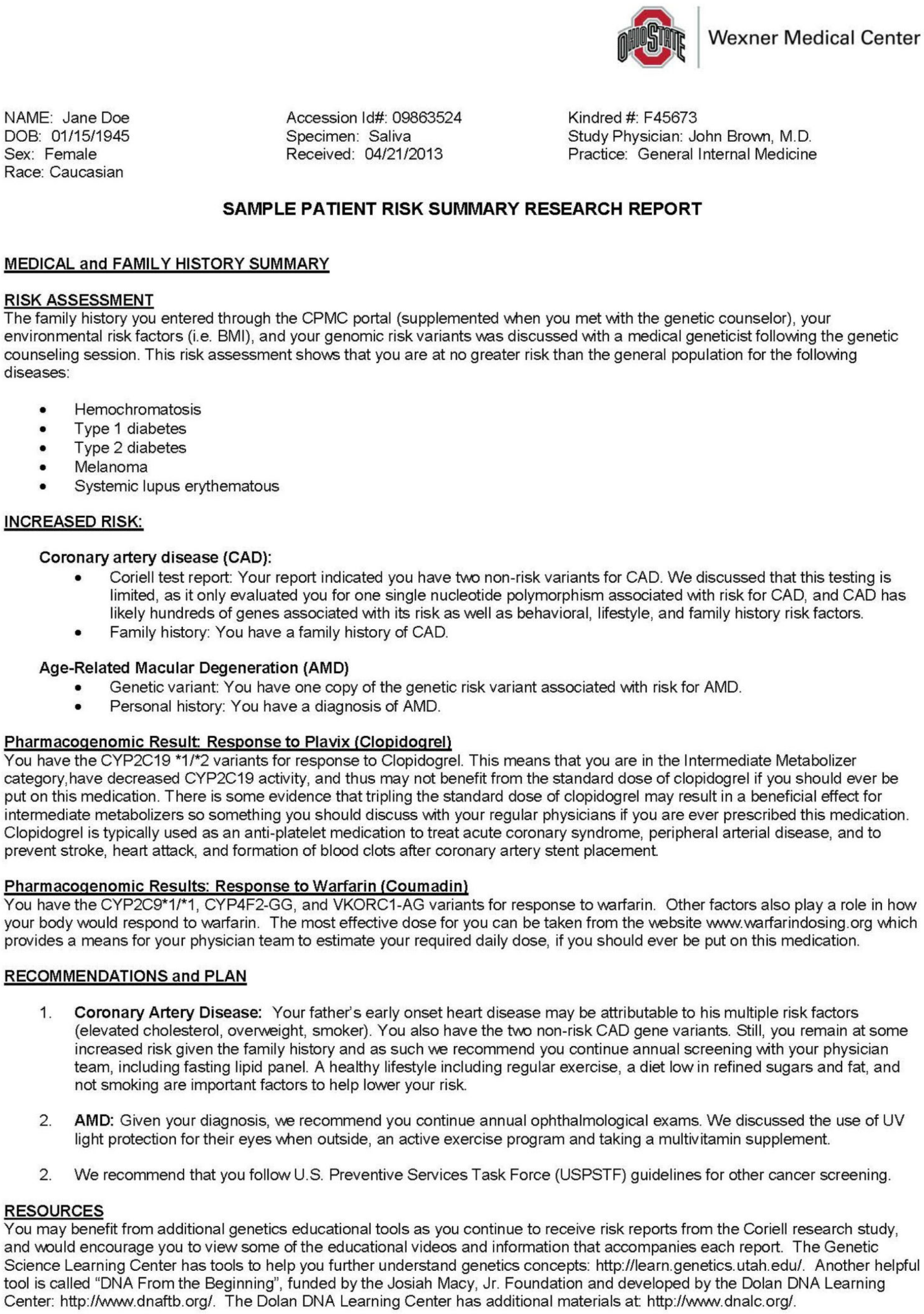
**Risk factors may be related to each other and risk estimates cannot be combined.**
**This graph provides a summary of the relative risks for genetic variant, family history diabetes and smoking status.**

**You reported you are a man, between 40 and 59 years old; 6% of men in your age group have coronary artery disease**

| Chart Color | Relative Risk Due To: | Your Risk | Baseline Risk | Maximum Risk | Interpretation |
|---|---|---|---|---|---|
| 🟩 | Genetic Variant | 1.3 | 1 | 1.7 | You have 1 copy of the risk variant and 1 copy of the non-risk variant. Based on this result, you are 30 % more likely (or 1.3 times as likely) to develop coronary artery disease as someone with no copies of this variant.<br>Having this risk variant contributes to your risk of coronary artery disease. |
| 🟪 | Family History | 1 | 1 | 1.4 | Based on your family history, you are at a lower risk to develop coronary artery disease compared to individuals who have one or both parents with coronary artery disease. |
| 🟦 | Diabetes | 1.7 | 1 | 1.7 | Because you reported that you have diabetes, you are 70% more likely (or 1.7 times as likely) to develop coronary artery disease as individuals without diabetes.<br>Having diabetes contributes to your risk of coronary artery disease. |
| 🟦 | Smoking Status | 2.1 | 1 | 2.1 | Because you are a smoker you are 2.1 times as likely to develop coronary artery disease as someone who is not a smoker.<br>Being a smoker contributes to your risk of coronary artery disease. |

**Figure 2.**

Sample CPMC® coronary artery disease report.



Wexner Medical Center

NAME: Jane Doe
DOB: 01/15/1945
Sex: Female
Race: Caucasian

Accession Id#: 09863524
Specimen: Saliva
Received: 04/21/2013

Kindred #: F45673
Study Physician: John Brown, M.D.
Practice: General Internal Medicine

**SAMPLE PATIENT RISK SUMMARY RESEARCH REPORT**

**MEDICAL and FAMILY HISTORY SUMMARY**

**RISK ASSESSMENT**

The family history you entered through the CPMC portal (supplemented when you met with the genetic counselor), your environmental risk factors (i.e. BMI), and your genomic risk variants was discussed with a medical geneticist following the genetic counseling session. This risk assessment shows that you are at no greater risk than the general population for the following diseases:

- Hemochromatosis
- Type 1 diabetes
- Type 2 diabetes
- Melanoma
- Systemic lupus erythematous

**INCREASED RISK:**

**Coronary artery disease (CAD):**

- Coriell test report: Your report indicated you have two non-risk variants for CAD. We discussed that this testing is limited, as it only evaluated you for one single nucleotide polymorphism associated with risk for CAD, and CAD has likely hundreds of genes associated with its risk as well as behavioral, lifestyle, and family history risk factors.
- Family history: You have a family history of CAD.

**Age-Related Macular Degeneration (AMD)**

- Genetic variant: You have one copy of the genetic risk variant associated with risk for AMD.
- Personal history: You have a diagnosis of AMD.

**Pharmacogenomic Result: Response to Plavix (Clopidogrel)**

You have the CYP2C19 *1/*2 variants for response to Clopidogrel. This means that you are in the Intermediate Metabolizer category,have decreased CYP2C19 activity, and thus may not benefit from the standard dose of clopidogrel if you should ever be put on this medication. There is some evidence that tripling the standard dose of clopidogrel may result in a beneficial effect for intermediate metabolizers so something you should discuss with your regular physicians if you are ever prescribed this medication. Clopidogrel is typically used as an anti-platelet medication to treat acute coronary syndrome, peripheral arterial disease, and to prevent stroke, heart attack, and formation of blood clots after coronary artery stent placement.

**Pharmacogenomic Results: Response to Warfarin (Coumadin)**

You have the CYP2C9*1/*1, CYP4F2-GG, and VKORC1-AG variants for response to warfarin. Other factors also play a role in how your body would respond to warfarin. The most effective dose for you can be taken from the website www.warfarindosing.org which provides a means for your physician team to estimate your required daily dose, if you should ever be put on this medication.

**RECOMMENDATIONS and PLAN**

1. **Coronary Artery Disease:** Your father's early onset heart disease may be attributable to his multiple risk factors (elevated cholesterol, overweight, smoker). You also have the two non-risk CAD gene variants. Still, you remain at some increased risk given the family history and as such we recommend you continue annual screening with your physician team, including fasting lipid panel. A healthy lifestyle including regular exercise, a diet low in refined sugars and fat, and not smoking are important factors to help lower your risk.

2. **AMD:** Given your diagnosis, we recommend you continue annual ophthalmological exams. We discussed the use of UV light protection for their eyes when outside, an active exercise program and taking a multivitamin supplement.

2. We recommend that you follow U.S. Preventive Services Task Force (USPSTF) guidelines for other cancer screening.

**RESOURCES**

You may benefit from additional genetics educational tools as you continue to receive risk reports from the Coriell research study, and would encourage you to view some of the educational videos and information that accompanies each report. The Genetic Science Learning Center has tools to help you further understand genetics concepts: http://learn.genetics.utah.edu/. Another helpful tool is called "DNA From the Beginning", funded by the Josiah Macy, Jr. Foundation and developed by the Dolan DNA Learning Center: http://www.dnaftb.org/. The Dolan DNA Learning Center has additional materials at: http://www.dnalc.org/.

**Figure 3.**

Sample patient risk summary research report.

## Table 1

Initial results: health conditions and relative risk based on SNP variant result.

| Health Condition | SNP | Reference Genotype (RR) | Heterozygote (RR) | Homozygote (RR) |
|---|---|---|---|---|
| Type 1 Diabetes | rs9272346 | GG (0.08) | GA (0.3) | AA (1.0) |
| Type 2 Diabetes | rs7754840 | GG (1.0) | GC (1.2) | CC (1.3) |
| Hemochromatosis | rs1800562 | GG (1.0) | AG (1.0)* | AA** |
| Systemic Lupus Erythematosus | rs3821236 | GG (1.0) | AG (1.4) | AA (2.0) |
| Coronary Artery Disease | rs1333049 | GG (1.0) | GC (1.3) | CC (1.7) |
| Prostate Cancer*** | rs16901979 | CC (1.0) | CA (1.5) | AA (1.5) |
| Skin Melanoma | rs910873 | CC (1.0) | CT (1.7) | TT (3.0) |
| Age Related Macular Degeneration | rs10490924 | GG (1.0) | GT (2.4) | TT (6.0) |

RR is relative risk

*Males Only, lifetime risk 4%

**Males with 2 copies of the risk variant (AA) are 27 times as likely to develop hemochromatosis RR = 27 (lifetime risk 57%). Females with GG or GA result have no relative risk provided, but are told they have up to a 1% lifetime risk. Females with AA result have no relative risk provided but are told they have a 16% lifetime risk of developing hemochromatosis

***Both male and female participants receive result report, with risk only applicable to male participants.

## Table 2

Additional Coriell Personalized Medicine Collaborative (CPMC®) approved health conditions for prospective release.

| **Health Condition** |
|---|
| • Breast Cancer |
| • Colorectal Cancer |
| • Ulcerative Colitis |
| • Crohn's Disease |
| • Obesity |
| • Rheumatoid Arthritis |
| • Testicular Cancer |
| • Chronic Obstructive |
| • Pulmonary Disease |
| • Bladder Cancer |
| • Celiac Disease |
| • Lung Cancer |
| • Osteoporosis |
| • Asthma |
| • Osteoarthritis |
| • Multiple Sclerosis |
| • Intracranial Aneurysm |
| • Exocrine Pancreatic Cancer |
| • Ischemic Stroke |

## Table 3

Additional CPMC® approved drug-gene pairs for prospective release.

| Drug-Gene Pairs |
|---|
| • CYP2C19/PPIs |
| • SLCO1B1/Simvastatin |
| • CYP2C9/Celecoxib |
| • TPMT/Thiopurines |
| • CYP2C9/Warfarin |
| • VKORC1/Warfarin |
| • CYP4F2/Warfarin |
| • CYP2D6/Codeine |
| • ATM/Metformin |
| • IL28A, IL28B, ITPA and Interferon/Ribavirin |
| • CYP2D6&CYP2C19/Amitriptyline/Nortriptyline |
| • CYP2D6/Paroxetin |

## Table 4

Cohort characteristics (n = 210).

| Characteristic | N |
|---|---|
| **Age (years)** | 58.1 |
| **Gender** | |
| Male | 117 |
| Female | 93 |
| **Race** | |
| Caucasian | 187 |
| African American | 16 |
| Native American | 1 |
| Mixed | 5 |
| Do not want to answer | 1 |
| **Education** | |
| <High School | 3 |
| High school | 17 |
| Vocational school | 1 |
| Some college | 45 |
| Associate degree | 26 |
| Bachelor degree | 50 |
| Graduate degree | 68 |